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Practical and efficient synthesis of chiral 2,4-disubstituted oxazolines from β-phosphonoamides

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ABSTRACT

Herein we report a practical and efficient method for the synthesis of optically active 2,4-disubstituted oxazolines (*S*)-**1a**–**h** in good to excellent yields. The target compounds were prepared in good yield through the Horner–Wadsworth–Emmons reaction of β-phosphonoamide **3** bearing L-phenylalaninol with commercially available aryl aldehydes followed by the cyclodehydration of the corresponding *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-**2a**–**h**. Additionally, the cyclodehydration of β-phosphonoamide (*S*)-**3** followed by the Horner–Wadsworth–Emmons reaction of β-phosphono-oxazoline (*S*)-**4** with aryl aldehydes also gave the 2,4-disubstituted oxazolines (*S*)-**1a**–**h**.

1. Introduction

For more than a century, heterocyclic compounds have constituted as one of the largest areas of research in organic chemistry. They have contributed to the development of society from a biological and industrial point of view, as well as to the understanding of life processes and to efforts to improve quality of life.[1] The presence of heterocycles in many types of organic compounds of interest in electronics, medicinal chemistry, and material science is very well known. Five-membered heterocyclic compounds containing nitrogen are privileged structures that are useful in synthetic and medicinal chemistry.[2,3] Among these, α,β-unsaturated oxazolines with five-membered rings containing nitrogen and oxygen, have received considerable attention in recent years, because these compounds are part of several natural products,[4] and also because they exhibit a wide range of biological and pharmacological activities such as antibacterial,[4c] antituberculosis,[5] antimalarial,[6] and anticancer.[7] Furthermore, α,β-oxazolines can be used as Michael acceptors for carbon-carbon bond formations, and can be transformed into alcohols, aldehydes, carboxylic acids, oxazole derivatives and used in the preparation of more complex compounds.[8] Additionally, chiral oxazolines have been widely used in asymmetric synthesis as both auxiliaries and ligands.[9,10] Due to their relevance, much effort has been dedicated to the preparation of oxazolines and their derivatives, including the cyclodehydration of β-hydroxyamides,[11] Passerini-Zhu/Staudinger-Aza-Wittig reaction,[12] and from nitriles,[13] carboxylic acids,[14] and aldehydes.[15] However, in spite of their potential utility, these methods typically suffer from one or more disadvantages such as harsh reaction conditions or tedious synthetic procedures. Due to the high value of these compounds in connection with our current research interest in the development of efficient and practical synthetic methods, we herein report a practical and efficient method for the synthesis of several new chiral 2,4-disubstituted oxazolines (*S*)-**1a**–**h**, with good to high yields from β-phosphonoamide (*S*)-**3**.

2. Results and discussion

For the synthesis of the target chiral 2,4-disubstituted oxazolines (*S*)-**1a**–**h**, two synthetic procedures were considered: (1) through the cyclodehydration of *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-**2**, which are readily obtained from the Horner–Wadsworth–Emmons reaction of β-phosphonoamide (*S*)-**3** with commercially available aryl aldehydes; and (2) by means of the Horner–Wadsworth–Emmons reaction of β-phosphono-oxazoline (*S*)-**4**, also obtained from β-phosphonoamide (*S*)-**3** (Scheme 1).

The synthetic sequence established in route A began with the preparation of β-phosphonoamide (*S*)-**3**, which was easily obtained using the recently described procedure in Ref. 16 Thus, the reaction of 2-diethyl-phosphonoacetic acid with L-phenylalaninol in the presence of dicyclohexylcarbodiimide (DCC) and catalytic amounts of 4-(dimethylamino)pyridine (DMAP) in dry dichloromethane at

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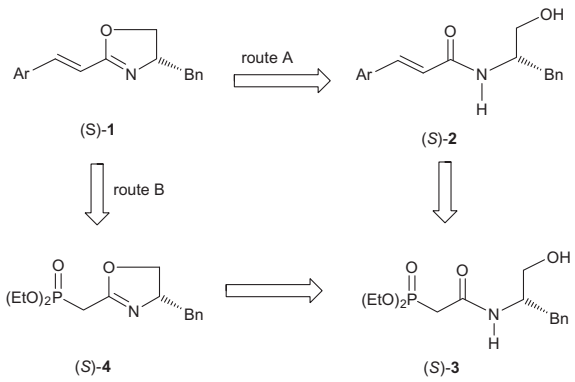
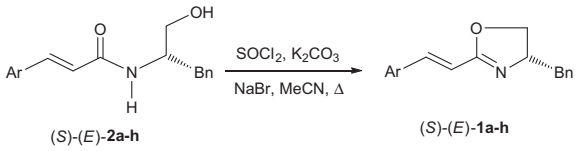


Scheme 1. β-Phosphonoamide (*S*)-**3** as the starting material for the synthesis of (*S*)-**1a–h**.

room temperature, afforded the β-phosphonoamide (*S*)-**3** in 94% yield. With compound **3** in hand and following a well-established protocol for the synthesis of α,β-unsaturated amides under Horner–Wadsworth–Emmons reaction conditions,[16,17] we decided to carry out the reaction of β-phosphonoamide (*S*)-**3** with benzaldehyde, using 8-diazabicyclo[5.4.0]undec-7-ene (DBU) as the base in the presence of LiCl in dry THF at room temperature, to obtain the corresponding *N*-(cinnamoyl)-(*S*)-phenylalaninol (*S*)-**2a** in 96% yield and a >98:2 ratio of *E*:*Z* (Table 1, entry 1). Similar results were obtained in the reaction of (*S*)-**3** with 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, and 4-methoxybenzaldehyde (Table 1, entries, 2, 3 and 5), and a moderate yield and excellent *E*:*Z* ratio were obtained in the reaction of compound (*S*)-**3** with 4-bromobenzaldehyde, 4-(benzyloxy)benzaldehyde, methyl 4-formylbenzoate, and 2-furaldehyde (Table 1, entries 4, 6-8). The *E*:*Z* ratio was determined by ^{1}H NMR spectroscopy on the crude product on the basis of the olefinic protons.

Once the *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-**2a–h** were synthesized, the scope of the cyclodehydration reaction was explored in order to obtain the target compounds (*S*)-**1a–h**. Initially, the reaction of compound (*S*)-**2a** with $SOCl_2$ was carried out in acetonitrile at reflux for 4 h in the presence of NaBr and K_2CO_3, to obtain the (4*S*)-4-benzyl-2-cinnamoyl-2-oxazoline (*S*)-**1a** in 60% yield (Table 2, entry 1). Similar results were obtained in the reaction of (*S*)-**2d**, and (*S*)-**2f–h** (Table 2, entries 4, 6–8), whereas the reaction of (*S*)-**2b** and (*S*)-**2c** under the same conditions afforded the 2,4-disubstituted oxazolines (*S*)-**1b** and (*S*)-**1c**, respectively, in low yields (Table 2, entries 2 and 3). Finally, the reaction of (*S*)-**2e** gave (*S*)-**1e** in 85% yield (Table 2, entry 5).

Table 2
Preparation of chiral 2,4-disubstituted oxazolines (*S*)-**1a–h**



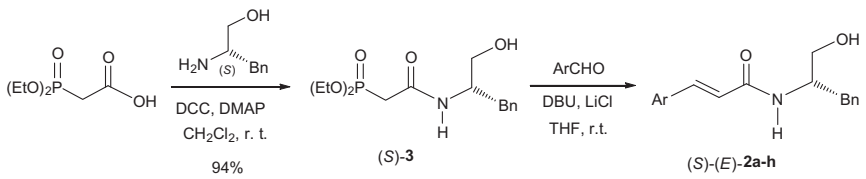
Entry	Product	Yield[a] (%)
1	**1a**; Ar = C_6H_5	60
2	**1b**; Ar = 4-FC_6H_4	30
3	**1c**; Ar = 4-ClC_6H_4	32
4	**1d**; Ar = 4-BrC_6H_4	64
5	**1e**; Ar = 4-$MeOC_6H_4$	85
6	**1f**; Ar = 4-$BnOC_6H_4$	64
7	**1g**; Ar = 4-$MeO_2CC_6H_4$	65
8	**1h**; Ar = 2-furfuryl	69

[a] Isolated after purification by column chromatography.

This procedure provided the target chiral 2,4-disubstituted oxazolines (*S*)-**1a–h**, although with only moderate yields. Consequently, route B was explored in order to obtain better results. In this context, and considering that the dehydrative cyclization of β-hydroxy amides is a conceptually simple and synthetically versatile approach for the synthesis of oxazolines, the reaction of β-phosphonoamide (*S*)-**3** with bis(2-methoxyethyl)amino-sulfur trifluoride (Deoxo-Fluor) as the cyclo dehydrating agent was carried out in the presence of K_2CO_3 with CH_2Cl_2 as the solvent at −20 °C, to obtain the desired β-phosphono-oxazoline (*S*)-**4** in 32% yield. After several attempts under different reaction conditions (varying the reaction times, temperatures, and equivalents of reagents), only a complex mixture of unidentified products was obtained. The low yield suggested the ineffectiveness of this strategy. For this reason, we decided to react β-phosphonoamide (*S*)-**3** with $SOCl_2$, NaBr, and Et_3N in CH_2Cl_2 at reflux, to give the β-bromo amide (*S*)-**5** in 80% yield, which upon the treatment with NaH in dry THF at room temperature, provided the desired β-phosphono-oxazoline (*S*)-**4** in 83% yield (Scheme 2).

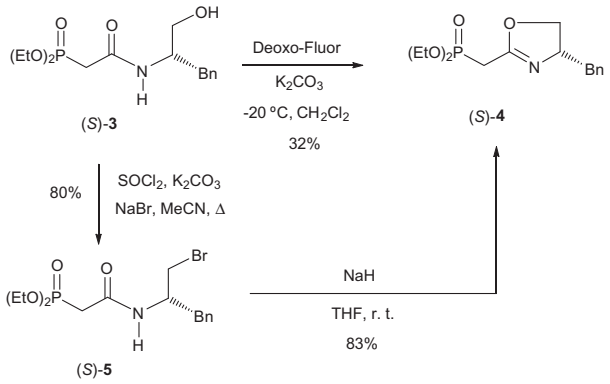
After preparation of phosphono-oxazoline (*S*)-**4**, the next step was to explore the scope of the Horner–Wadsworth–Emmons reaction in order to obtain chiral 2,4-disubstituted oxazolines (*S*)-**1**. In this context, we carried out the reaction of (*S*)-**4** with

Table 1
Preparation of *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-**2a–h**



Entry	Product	Yield[a] (%)
1	**2a**; Ar = C_6H_5	96
2	**2b**; Ar = 4-FC_6H_4	96
3	**2c**; Ar = 4-ClC_6H_4	98
4	**2d**; Ar = 4-BrC_6H_4	80
5	**2e**; Ar = 4-$MeOC_6H_4$	95
6	**2f**; Ar = 4-$BnOC_6H_4$	64
7	**2g**; Ar = 4-$MeO_2CC_6H_4$	54
8	**2h**; Ar = 2-furfuryl	71

[a] Isolated after purification by column chromatography.



Scheme 2.

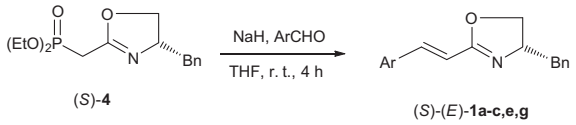
benzaldehyde, DBU, and LiCl in THF at room temperature. However, after 4 h, only a small amount of the 2,4-disubstituted oxazoline (*S*)-**1a** was obtained, along with the starting material.

In view of the unsatisfactory results for the synthesis of the 2,4-disubstituted oxazoline (*S*)-**1a** under these conditions, the Horner–Wadsworth–Emmons reaction of the phosphono-oxazoline (*S*)-**4** was performed with benzaldehyde using NaH as the base in THF at room temperature for 4 h, to give the 2,4-disubstituted oxazoline (*S*)-**1a** in 30% yield. Similar results were obtained in the reaction of (*S*)-**4** with 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, 4-methoxybenzaldehyde, and methyl 4-formylbenzoate, (Table 3, entries 2–5). It was noted that when the reaction was carried out at temperatures above 35 °C, several unidentified products were formed. Additionally, we found that the phosphono-oxazoline (*S*)-**4** appeared to be unstable for long reaction times and gave unidentified compounds.

After these results, we next turned our attention to the sequential cyclo dehydrohalogenation and Horner–Wadsworth–Emmons reaction. For this purpose, the procedure reported by Shukla et al.[18] was followed. Thus, the reaction of β-bromo amide (*S*)-**5** was carried out in the presence of K_2CO_3 as the base in dimethylformamide (DMF) at reflux to afford the phosphono-oxazoline (*S*)-**4**, which without additional purification, was treated with benzaldehyde and refluxed for 2 h to obtain the 2,4-disubstituted oxazoline (*S*)-**1a** in 93% yield (Table 4, entry 1). Similar results were obtained in the reaction of (*S*)-**5** with 4-fluorobenzaldehyde, 4-chlorobenzaldehyde, methyl 4-formylbenzoate, and 2-furaldehyde (Table 4, entries 2, 3, 7 and 8). Moderate yields were obtained in the reaction of (*S*)-**5** with 4-bromobenzaldehyde, 4-methoxybenzaldehyde, and 4-(benzyloxy)benzaldehyde (Table 4, entries 4–6).

As can be seen in Table 4, a significant improvement in chemical yields was found when applying this methodology to obtain the target compounds (*S*)-**1a–h**. Additionally, no loss in the enantiomeric purity of chiral 2,4-disubstituted oxazolines (*S*)-**1a–h** was found in this process, in which the specific rotations were compared with those obtained in the above experiments.

Table 3
Synthesis of chiral 2,4-disubstituted oxazolines (*S*)-**1** from (*S*)-**4**



Entry	Product	Yield[a] (%)
1	**1a**; Ar = C_6H_5	30
2	**1b**; Ar = 4-FC_6H_4	15
3	**1c**; Ar = 4-ClC_6H_4	32
4	**1e**; Ar = 4-$MeOC_6H_4$	34
5	**1g**; Ar = 4-$MeO_2CC_6H_4$	47

[a] Isolated after purification by column chromatography.

3. Conclusion

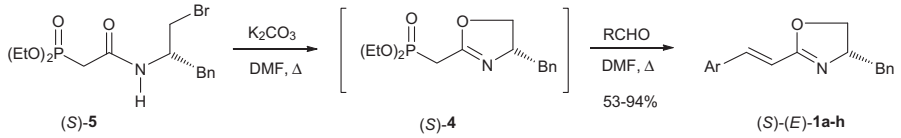
In conclusion, we have established a practical and efficient methodology for the synthesis of chiral 2,4-disubstituted oxazolines (*S*)-**1a–h** through the Horner–Wadsworth–Emmons reaction of β-phosphonoamide (*S*)-**3** bearing L-phenylalaninol with several aryl aldehydes, followed by the cyclodehydration of the *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-**2a–h**, and by sequential cyclodehydro-halogenation and Horner–Wadsworth–Emmons reaction of (*S*)-**5**. This report represents an easy access to chiral 2,4-disubstituted oxazolines (*S*)-**1a–h**. Studies on the biological activity of these oxazolines are currently in progress.

4. Experimental

4.1. General

All commercial materials were used as received unless noted otherwise. Anhydrous solvents (ethers) were obtained by distillation from benzophenone ketyl. Melting points were registered using an Electrothermal II apparatus and are uncorrected. Flash chromatography was performed using 230–400 mesh Silica Flash 60® silica gel. Thin layer chromatography was carried out on precoated TLC sheets of silica gel 60 F254 (E. Merck). NMR spectra

Table 4
Synthesis of chiral 2,4-disubstituted oxazolines (*S*)-**1a–h** from (*S*)-**5**



Entry	Product	Yield[a] (%)
1	**1a**; Ar = C_6H_5	93
2	**1b**; Ar = 4-FC_6H_4	93
3	**1c**; Ar = 4-ClC_6H_4	94
4	**1d**; Ar = 4-BrC_6H_4	80
5	**1e**; Ar = 4-$MeOC_6H_4$	68
6	**1f**; Ar = 4-$BnOC_6H_4$	53
7	**1g**; Ar = 4-$MeO_2CC_6H_4$	89
8	**1h**; Ar = 2-furfuryl	94

[a] Isolated after purification by column chromatography and only the *E* isomer was detected by ^1H NMR.

were recorded on two Varian System instruments (400 MHz for ^{1}H, 161 MHz for ^{31}P and 100 MHz for ^{13}C, and 300 MHz for ^{1}H, 121 for ^{31}P and 75 MHz for ^{13}C), as well as on a Mercury instrument (200 MHz for ^{1}H and 81 for ^{31}P). The spectra were obtained in $CDCl_3$ and DMSO-d_6 solution using TMS as an internal reference. Chemical shifts (δ) are reported in parts per million. Multiplicities are recorded as follows: s = singlet, d = doublet, t = triplet, dd = doublet of doublets, td = triplet of doublets, bs = broad signal, q = quartet and m = multiplet. Coupling constants (J) are given in Hz. High resolution FAB$^+$ mass experiments were done on a JEOL HRMStation JHRMS-700. Optical rotations were measured at 28 °C on an Anton-Paar MCP 300 polarimeter in a 2.5 mm cell.

4.2. (*S*)-2-(2-Diethoxyphosphoryl)acetamide-3-phenyl-propanol (*S*)-3

A solution of dicyclohexylcarbodiimide (4.15 g, 20.2 mol) and 4-(dimethylamino)pyridine (490 mg, 4.02 mmol) in 100 mL of dry dichloromethane was slowly added at room temperature to a solution of 2-diethyl-phosphonoacetic acid (4.37 g, 22.3 mmol) and (*S*)-2-amino-3-phenyl-1-propanol (3.1 g, 20.2 mmol) in 100 mL of anhydrous CH_2Cl_2 under an inert atmosphere. The reaction mixture was stirred at room temperature for 12 h, filtered, and washed with AcOEt (20 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography on silica gel AcOEt–Hex–MeOH (5:4:1), to obtain compound (*S*)-**3** (6.6 g, 94% yield) as a viscous oil, $[\alpha]_D = -16.5$ (c 1.7, MeOH). ^{1}H and ^{13}C NMR data are identical with those described in the literature.[19] HRMS (FAB$^+$): calculated for $C_{15}H_{25}NO_5P$ $[M+H]^+$, m/z 330.1470; found for $[M+H]^+$, m/z 330.1467.

4.3. (*S*)-2-(2-Diethoxyphosphoryl)acetamide-3-phenyl-bromoprapane (*S*)-5

Thionyl chloride (0.88 mL, 12.3 mmol) was added dropwise to a solution of (*S*)-**3** (2.02 g, 6.1 mmol) and Et_3N (0.85 mL, 6.1 mmol) in anhydrous CH_2Cl_2 (30 mL). The reaction mixture was stirred for 15 min at reflux followed by the addition of NaBr (940 mg, 9.2 mmol). The reaction mixture was then stirred at reflux for 3 h. After this time, the reaction was quenched by the addition of a saturated NH_4Cl solution (10 mL), and extracted with AcOEt (3 × 30 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography AcOEt–Hex–MeOH (5:4:1), to obtain compound (*S*)-**5** (1.91 g, 80% yield) as a white solid, mp 89–91 °C, $[\alpha]_D = -12.9$ (c 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (t, J = 7.2 Hz, 3H, $(CH_3CH_2O)_2P$), 1.34 (t, J = 7.2 Hz, 3H, $(CH_3CH_2O)_2P$), 2.82 (dd, $J_{H/P}$ = 17.8, J_{gem} = 15.5 Hz, 1H, CH_2P), 2.87 (dd, $J_{H/P}$ = 17.8, J_{gem} = 15.5 Hz, 1H, CH_2P), 2.94 (d, J = 7.8 Hz, 2H, CH_2Ph), 3.51 (dd, J = 11.3, 3.5 Hz, 1H, CH_2Br), 3.64 (dd, J = 11.3, 4.1 Hz, 1H, CH_2Br), 4.06 (dq, J = 14.2, 7.1 Hz, 2H, CH_2OP), 4.15 (dq, J = 14.2, 7.1 Hz, 2H, CH_2OP), 4.42–4.50 (m, 1H, CHBn), 7.10 (d, J = 8.0 Hz, 1H, NH), 7.21–7.33 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.4 ($(CH_3CH_2O)_2P$), 16.5 ($(CH_3CH_2O)_2P$), 35.2 (d, J = 131.0 Hz, CH_2P), 37.5 (CH_2Ph), 46.5 (CH_2Br), 51.5 (CHBn), 62.9 (d, J = 3.7 Hz, CH_2OP), 63.0 (d, J = 3.7 Hz, CH_2OP), 127.0, 128.9, 129.4, 137.0, 163.9 (C=O). ^{31}P NMR (161 MHz, $CDCl_3$): δ 22.46.

4.4. General procedure for the preparation of *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-2a–h

A solution of β-phosphonoamide (*S*)-**3** (1.0 equiv) in dry THF (30 mL) was treated under a nitrogen atmosphere with 8-diazabicyclo[5.4.0]undec-7-ene (3.0 equiv). The mixture was stirred at room temperature for 30 min, prior to the addition of the corresponding aldehyde (1.0 equiv), after which it was stirred at room temperature for 4 h. The reaction was quenched by the addition of a saturated NH_4Cl solution (10 mL), and extracted with AcOEt (3 × 30 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography using Hex-AcOEt (7:3) and ethyl acetate-hexane-methanol (5:4:1).

4.4.1. *N*-(Cinnamoyl)-(*S*)-phenylalaninol (*S*)-2a

(300 mg, 96%) as a white solid, mp 144–146 °C, $[\alpha]_D = -100.0$ (c 1.0, MeOH). ^{1}H and ^{13}C NMR data are identical with those described in the literature.[11c] HRMS (FAB$^+$): calculated for $C_{18}H_{20}NO_2$ $[M+H]^+$, m/z 282.1494; found for $[M+H]^+$, m/z 282.1506.

4.4.2. *N*-(*p*-Fluorocinnamoyl)-(*S*)-phenylalaninol (*S*)-2b

(470 mg, 96%) as a solid, mp 75–77 °C, $[\alpha]_D = -88.3$ (c 1.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.92 (d, J = 7.2 Hz, 2H, CH_2Ph), 3.62 (dd, J = 11.2, 5.2 Hz, 1H, CH_2OH), 3.72 (dd, J = 11.2, 3.8 Hz, 1H, CH_2OH), 4.31 (m, 1H, CHBn), 6.28 (d, J_{trans} = 15.6 Hz, 1H, CHC=O), 6.38 (d, J = 7.6 Hz, 1H, NH), 6.9 (dd, J = 8.8, 7.2 Hz, 2H, H_{arom}), 7.20–7.29 (m, 5H, H_{arom}), 7.37 (dd, J = 8.4, 5.2 Hz, 2H, H_{arom}), 7.50 (d, J_{trans} = 15.6 Hz, 1H, CH(*p*-FC_6H_4)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.2 (CH_2Ph), 53.2 (CHBn), 64.0 (CH_2OH), 116.0, 120.37 (CH), 126.8, 128.8, 129.4, 129.8, 131.0, 137.8, 140.4 (CH), 163.7, 166.6 (C=O). HRMS (FAB$^+$): calculated for $C_{18}H_{19}NO_2F$ $[M+H]^+$, m/z 300.1400; found for $[M+H]^+$, m/z 300.1402.

4.4.3. *N*-(*p*-Chlorocinnamoyl)-(*S*)-phenylalaninol (*S*)-2c

(260 mg, 98%) as a solid, mp 132–134 °C, $[\alpha]_D = -1.3$ (c 3.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.88 (dd, J = 13.9, 7.2 Hz, 1H, CH_2Ph), 2.94 (dd, J = 13.9, 7.3 Hz, 1H, CH_2Ph), 3.56 (dd, J = 11.3, 5.2 Hz, 1H, CH_2OH), 3.64 (dd, J = 11.3, 4.2 Hz, 1H, CH_2OH), 4.19–4.34 (m, 1H, CHBn), 6.46 (d, J_{trans} = 15.7 Hz, 1H, CHC=O), 7.15–7.44 (m, 10H, H_{arom} and NH), 7.49 (d, J_{trans} = 15.7 Hz, 1H, CH(*p*-ClC_6H_4)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 36.9 (CH_2Ph), 52.8 (CHBn), 63.0 (CH_2OH), 121.2, 126.4, 128.4, 129.0 (2), 129.2, 133.4, 135.5, 137.9, 139.6, 166.6 (C=O). HRMS (FAB$^+$): calculated for $C_{18}H_{19}NO_2Cl$ $[M+H]^+$, m/z 316.1104; found for $[M+H]^+$, m/z 316.1105.

4.4.4. *N*-(*p*-Bromocinnamoyl)-(*S*)-phenylalaninol (*S*)-2d

(990 mg, 80%) as a solid, mp 168–169 °C, $[\alpha]_D = -110.8$ (c 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.89 (dd, J = 7.2, 2.8 Hz, 1H, CH_2Ph), 2.91 (dd, J = 7.2, 2.8 Hz, 1H, CH_2Ph), 3.56 (dd, J = 11.2, 5.2 Hz, 1H, CH_2OH), 3.66 (dd, J = 11.2, 4.0 Hz, 1H, CH_2OH), 4.27 (m, 1H, CHBn), 6.40 (d, J_{trans} = 15.6 Hz, 1H, CHC=O), 6.94 (d, J = 8.0 Hz, 1H, NH), 7.18–7.31 (m, 7H, H_{arom}), 7.43-7.48 (m, 3H, H_{arom} and CH(*p*-BrC_6H_4)). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0 (CH_2-Ph), 52.8 (CHBn), 63.2 (CH_2OH), 121.3 (CH), 121.4, 123.9, 126.6, 128.6, 129.2, 132.0, 133.7, 137.9, 139.8 (CH), 166.5 (C=O). HRMS (FAB$^+$): calculated for $C_{18}H_{19}NO_2Br$ $[M+H]^+$, m/z 360.0599; found for $[M+H]^+$, m/z 360.0590.

4.4.5. *N*-(*p*-Methoxycinnamoyl)-(*S*)-phenylalaninol (*S*)-2e

(300 mg, 95%) as a solid, mp 128–130 °C, $[\alpha]_D = -95.7$ (c 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.91 (dd, J = 14.1, 7.6 Hz, 1H, CH_2Ph), 2.98 (dd, J = 14.1, 7.6 Hz, 1H, CH_2Ph), 3.60 (dd, J = 11.2, 5.1 Hz, 1H, CH_2OH), 3.67 (dd, J = 11.2, 4.3 Hz, 1H, CH_2OH), 3.78 (s, 3H, CH_3O), 4.26–4.34 (m, 2H, CHBn and NH), 6.40 (d, J_{trans} = 15.7 Hz, 1H, CHC=O), 6.85 (d, J = 8.7 Hz, 2H, H_{arom}), 7.31–7.13 (m, 5H, H_{arom}), 7.42 (d, J = 8.7 Hz, 2H, H_{arom}), 7.51 (d, J_{trans} = 15.7 Hz, 1H, CH(*p*-$CH_3OC_6H_4$)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 36.6 (CH_2Ph), 52.5 (CHBn), 54.8 ($CH_3OC_6H_4$), 62.6 (CH_2OH), 113.7, 117.7, 125.8, 126.9, 127.8, 128.7, 128.8, 137.6, 140.0, 160.3, 166.7

(C=O). HRMS (FAB$^+$): calculated for $C_{19}H_{22}NO_3$ [M+H]$^+$, m/z 312.1600; found for [M+H]$^+$, m/z 312.1587.

4.4.6. *N*-(*p*-Benzyloxycinnamoyl)-(*S*)-phenylalaninol (*S*)-2f

(380 mg, 64%) as a solid, mp 171-173 °C, $[\alpha]_D = -83.35$ (c 1.0, DMSO). ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.69 (dd, J = 13.7, 8.5 Hz, 1H, CH_2Ph), 2.90 (dd, J = 13.7, 5.6 Hz, 1H, CH_2Ph), 3.36 (dd, J = 10.7, 5.6 Hz, 1H, CH_2OH), 3.42 (dd, J = 10.8, 4.9 Hz, 1H, CH_2OH), 3.94–4.12 (m, 1H, CHBn), 5.13 (s, 2H, OCH_2Ph), 6.52 (d, J_{trans} = 15.9, 1H, CHC=O), 7.04 (d, J = 8.7, 2H, H_{arom}), 7.31 (d, J_{trans} = 15.9, 1H, CH(*p*-$BnOC_6H_4$), 7.12–7.53 (m, 10H, H_{arom}), 7.48 (d, J = 8.8 Hz, 2H, H_{arom}), 8.03 (d, J = 8.3 Hz, 1H, NH). ^{13}C NMR (75 MHz, CD_3OD): δ 36.7 (CH_2Ph), 52.5 (CHBn), 62.8 (CH_2OH), 69.9 (OCH_2Ph), 114.9, 118.0, 126.2, 127.3, 127.5, 127.8, 128.2, 128.4, 129.0, 129.1, 136.3, 137.8, 140.5, 159.9, 167.1 (C=O). HRMS (FAB$^+$): calculated for $C_{25}H_{26}NO_3$ [M+H]$^+$, m/z 388.1913; found for [M+H]$^+$, m/z 388.1910.

4.4.7. *N*-(*p*-Carbomethoxycinnamoyl)-(*S*)-phenylalaninol (*S*)-2g

(580 mg, 54%) as a solid, mp 161–163 °C, $[\alpha]_D = -116.0$ (c 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (dd, J = 13.6, 7.0 Hz, 1H, CH_2Ph), 2.95 (dd, J = 13.6, 7.2 Hz, 1H, CH_2Ph), 3.57 (dd, J = 11.2, 5.2 Hz, 1H, CH_2OH), 3.67 (dd, J = 11.2, 4.0 Hz, 1H, CH_2OH), 3.91 (s, 3H, CH_3O), 4.28 (m, 1H, CHBn), 6.52 (d, J_{trans} = 15.6 Hz, 1H, CHC=O), 7.08 (d, J = 8.0 Hz, 1H, NH), 7.18–7.31 (m, 5H, H_{arom}), 7.49 (d, J = 8.4 Hz, 2H, H_{arom}). 7.55 (d, J_{trans} = 15.6 Hz 1H, CH(*p*-$CH_3O_2CC_6H_4$)), 7.98 (d, J = 8.4 Hz, 2H, H_{arom}), ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.0 (CH_2Ph), 52.3 (CH_3O), 52.9 (CHBn), 63.2 (CH_2OH), 123.2 (CH), 126.6, 127.7, 128.6, 129.3, 130.1, 130.7, 137.9, 139.3, 139.7 (CH), 166.3 (C=O), 166.9 (C=O). HRMS (FAB$^+$): calculated for $C_{20}H_{22}NO_4$ [M+H]$^+$, m/z 340.1549; found for [M+H]$^+$, m/z 340.1556.

4.4.8. *N*-(Furan-2-yl-acryloyl)-(*S*)-phenylalaninol (*S*)-2h

(380 mg, 71%) as a solid, mp 111–113 °C, $[\alpha]_D = -116.0$ (c 1.0, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.91 (d, J = 7.3 Hz, 2H, CH_2Ph), 3.60 (dd, J = 11.2, 5.3 Hz, 1H, CH_2OH), 3.70 (dd, J = 11.2, 3.8 Hz, 1H, CH_2OH), 4.29 (m, 1H, CHBn), 6.28 (d, J_{trans} = 15.3 Hz, 1H, CHC=O), 6.37 (d, J = 8.0, 1H, NH), 6.39 (dd, J = 3.4, 1.8 Hz, 1H, CH=CH–O), 6.49 (d, J = 3.4 Hz, 1H, CH=C), 7.34 (d, J_{trans} = 15.3 Hz, 1H, CH-furyl), 7.14–7.37 (m, 6H, H_{arom} and CH-O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.2 (CH_2Ph), 53.2 (CHBn), 64.0 (CH_2OH), 112.3, 114.2, 118.3, 126.8, 128.4, 128.7, 129.4, 137.8, 144.3, 151.3, 166.7 (C=O). HRMS (FAB$^+$): calculated for $C_{16}H_{18}NO_3$ [M+H]$^+$, m/z 272.1287; found for [M+H]$^+$, m/z 272.1282.

4.5. (*S*)-Diethyl ((4-benzyl-4,5-dihydrooxazol-2-yl)methyl)phosphonate (*S*)-4

A suspension of NaH (130 mg, 5.6 mmol) in anhydrous THF (25 mL) was added to a solution of (*S*)-**5** (1.0 g, 2.5 mmol) in dry THF (15 mL). The reaction mixture was stirred at room temperature under an inert atmosphere for 12 h. After this time, the reaction mixture was quenched by the addition of a saturated NH_4Cl solution (10 mL), and extracted with AcOEt (3 × 30 mL). The organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by flash chromatography AcOEt-Hex-MeOH (5:4:1), to obtain compound (*S*)-**4** (670 mg. 83% yield) as a yellow oil, $[\alpha]_D = -42.9$ (c 4.7, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.35 (t, J = 6.8 Hz, 6H, $(CH_3CH_2O)_2P$), 2.93 (d, J = 21.5 Hz, 2H, CH_2P), 2.66 (dd, J = 13.8, 8.5 Hz, 1H, CH_2Ph), 3.10 (dd, J = 13.8, 5.5 Hz, 1H, CH_2Ph), 4.02 (dd, J = 8.3, 7.5 Hz, 1H, CH_2O), 4.24 (dd, J = 9.1, 8.8 Hz, 1H, CH_2O), 4.17 (dq, J = 14.4, 7.1 Hz, 4H, CH_2OP), 4.37–4.46 (m, 1H, CHBn), 7.19–7.32 (m, 5H, H_{arom}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.4 (($CH_3CH_2O)_2P$), 16.4 (($CH_3CH_2O)_2P$), 27.4 (d, J = 138.6 Hz, CH_2P), 41.6 (CH_2Ph), 62.7 (d, J = 5.3 Hz, CH_2OP), 67.6 (CHBn), 72.4 (CH_2O), 126.7, 128.6, 129.2, 137.8, 160.4 (d, J = 8.9 Hz, C=N). ^{31}P NMR (161 MHz, $CDCl_3$) δ: 21.13. HRMS (FAB$^+$): calculated for $C_{15}H_{23}NO_4P$ [M+H]$^+$, m/z 312.1365; found for [M+H]$^+$, m/z 312.1363.

4.6. General procedure for the preparation of chiral 2,4-disubstituted oxazolines (*S*)-1a–h from (*S*)-2a–h

A solution of *N*-(cinnamoyl)-(*S*)-phenylalaninol derivatives (*S*)-**2a–h** in CH_3CN (30 mL) was treated with $SOCl_2$ (1.1 equiv), K_2CO_3 (2.2 equiv), and NaBr (1.0 equiv). The reaction mixture was stirred at reflux for 4 h. After this time, the reaction mixture was quenched by the addition of a saturated NH_4Cl solution (15 mL). The solvent was evaporated under reduced pressure and the remaining residues were dissolved in water (30 mL) and extracted with AcOEt (3 × 30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography using Hex–AcOEt (7:3).

4.7. General procedure for the preparation of chiral 2,4-disubstituted oxazolines (*S*)-1a–c,e,h from (*S*)-4a–c,e,h using NaH as a base

A suspension of NaH (2.2 equiv) in anhydrous THF (25 mL) was added dropwise to a solution of (*S*)-**4** (1.0 equiv) in dry THF (15 mL). The mixture was stirred under an inert atmosphere at room temperature for 30 min, prior to the addition of the corresponding aldehyde (1.0 equiv). The resulting mixture was stirred at room temperature for 4 h. After this time, the reaction was quenched by the addition of a saturated NH_4Cl solution (10 mL), and extracted with AcOEt (3 × 30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography using Hex-AcOEt (7:3).

4.8. General procedure for the preparation of chiral 2,4-disubstituted oxazolines (*S*)-1a–h from (*S*)-5 using K_2CO_3 as a base

A mixture of (*S*)-**5** (1.0 equiv) and K_2CO_3 (2.0 equiv) in dry DMF (5 mL) was stirred at reflux for 2 h prior to the addition of the corresponding aldehyde (1.0 equiv), and then stirred at reflux for an additional 2 h. The reaction mixture was quenched by the addition of a saturated NH_4Cl solution (15 mL) and extracted with AcOEt (3 × 30 mL). The organic extracts were combined, dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. The crude product was purified by column chromatography using Hex–AcOEt (7:3).

4.8.1. (4*S*)-4-Benzyl-2-cinnamoyl-2-oxazoline (*S*)-1a

(273 mg, 93%) as a white solid, mp 71-73 °C, $[\alpha]_D = -10.0$ (c 1.0, MeOH). ^{1}H and ^{13}C NMR data are identical with those described in the literature.[11c] HRMS (FAB$^+$): calculated for $C_{18}H_{18}NO$ [M+H]$^+$, m/z 264.1388; found for [M+H]$^+$, m/z 264.1400.

4.8.2. (4*S*)-4-Benzyl-2-(*p*-fluorocinnamoyl)-2-oxazoline (*S*)-1b

(279 mg, 93%) as a white solid, mp 93–95 °C, $[\alpha]_D = +17.7$ (c 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.91 (dd, J = 13.7, 8.5 Hz, 1H, CH_2Ph), 3.35 (dd, J = 13.7, 8.5 Hz, 1H, CH_2Ph), 4.25 (t, J = 7.4 Hz, 1H, CH_2O), 4.49 (t, J = 8.4 Hz, 1H, CH_2O), 4.72 (m, 1H, CHBn), 6.75 (d, J_{trans} = 16.2 Hz, 1H, CHC=N), 7.20–7.24 (m, 1H, H_{arom}), 7.32 (d, J_{trans} = 16.2 Hz, 1H, CH(*p*-FC_6H_4)), 7.45–7.65 (m, 7H, H_{arom}), 7.67–7.68 (m, 1H, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.8 (CH_2Ph), 67.8 (CHBn), 71.6 (CH_2O), 114.9 (CH), 115.8 (CH), 116.0 (CH), 126.5, 128.6, 129.2, 131.4, 137.9, 138.7, 163.0, 163.6 (C=N). HRMS

(FAB$^+$): calculated for $C_{18}H_{17}NOF$ [M+H]$^+$, *m*/*z* 282.1294; found for [M+H]$^+$, *m*/*z* 282.1304.

4.8.3. (4*S*)-4-Benzyl-2-(*p*-chlorocinnamoyl)-2-oxazoline (*S*)-1c

(240 mg, 94%) as a white solid, mp 81–83 °C, $[\alpha]_D$ = +4.0 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (dd, *J* = 13.8, 8.4 Hz, 1H, CH_2Ph), 3.14 (dd, *J* = 13.8, 5.4 Hz, 1H, CH_2Ph), 4.04 (dd, *J* = 8.4, 7.8 Hz, 1H, CH_2O), 4.27 (dd, *J* = 9.0, 8.4 Hz, 1H, CH_2O), 4.48 (m, 1H, CHBn), 6.63 (d, J_{trans} = 16.2, 1H, CHC=N), 7.21-7.51 (m, 10H, H_{arom} and CH(*p*-ClC_6H_4)). ^{13}C NMR (75 MHz, $CDCl_3$):δ 41.7 (CH_2Ph), 67.7 (CHBn), 71.6 (CH_2O), 115.8 (CH), 123.6, 126.5, 128.6, 128.8, 129.1, 132.0, 134.1, 137.8, 138.7 (CH), 163.4 (C=N). HRMS (FAB$^+$): calculated for $C_{18}H_{17}NOCl$ [M+H]$^+$, *m*/*z* 298.0999; found for [M+H]$^+$, *m*/*z* 298.1002.

4.8.4. (4*S*)-4-Benzyl-2-(*p*-bromocinnamoyl)-2-oxazoline (*S*)-1d

(250 mg, 80%) as a white solid, mp 98–99 °C, $[\alpha]_D$ = +8.0 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.70 (dd, *J* = 13.8, 8.4 Hz, 1H, CH_2Ph), 3.14 (dd, *J* = 13.8, 5.7 Hz, 1H, CH_2Ph), 4.03 (dd, *J* = 8.2, 7.8 Hz, 1H, CH_2O), 4.26 (dd, *J* = 9.0, 8.2 Hz, 1H, CH_2O), 4.50 (m, 1H, CHBn), 6.60 (d, J_{trans} = 16.2 Hz, 1H, CHC=N), 7.21–7.42 (m, 10H, H_{arom} and CH(*p*-BrC_6H_4)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.7 (CH_2Ph), 67.7 (CHBn), 71.6 (CH_2O), 115.7 (CH), 126.5, 128.3, 128.7, 128.8, 129.1, 133.6, 135.3, 137.8, 138.6 (CH), 163.5 (C=N). HRMS (FAB$^+$): calculated for $C_{18}H_{17}NOBr$ [M+H]$^+$, *m*/*z* 342.0494; found for [M+H]$^+$, *m*/*z* 342.0489.

4.8.5. (4*S*)-4-Benzyl-2-(*p*-methoxycinnamoyl)-2-oxazoline (*S*)-1e

(200 mg, 68%) as a white solid, mp 68–70 °C, $[\alpha]_D$ = +16.3 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (dd, *J* = 13.8, 8.7 Hz, 1H, CH_2-Ph), 3.16 (dd, *J* = 13.8, 4.8 Hz, 1H, CH_2Ph), 3.80 (s, 3H, CH_3O), 4.03 (dd, *J* = 8.1, 7.5 Hz, 1H, CH_2O), 4.26 (dd, *J* = 8.7, 8.1 Hz, 1H, CH_2O), 4.50 (m, 1H, CHBn), 6.52 (d, J_{trans} = 16.2 Hz, 1H, CHC=N), 7.32 (d, *J* = 6.9 Hz, 2H, H_{arom}), 7.22-7.43 (m, 8H, H_{arom} and CH(*p*-CH_3OC_6-H_4)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.8 (CH_2Ph), 55.3 (CH_3O), 67.6 (CHBn), 71.5 (CH_2O), 112.7 (CH), 114.2, 126.5, 127.9, 128.5, 128.9, 129.1, 138.0, 139.7 (CH), 160.7, 164.0 (C=N). HRMS (FAB$^+$): calculated for $C_{19}H_{20}NO_2$ [M+H]$^+$, *m*/*z* 294.1494; found for [M+H]$^+$, *m*/*z* 294.1490.

4.8.6. (4*S*)-4-Benzyl-2-(*p*-benzyloxycinnamoyl)-2-oxazoline (*S*)-1f

(140 mg, 53%) as a white solid, mp 141–143 °C, $[\alpha]_D$ = +23.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ (dd, *J* = 13.8, 9.0 Hz, 1H, CH_2Ph), 3.16 (dd, *J* = 13.5, 5.1 Hz, 1H, CH_2Ph), 4.03 (dd, *J* = 8.2, 7.5 Hz, 1H, CH_2O), 4.27 (dd, *J* = 9.3, 8.2 Hz, 1H, CH_2O), 4.49 (m, 1H, CHBn), 5.08 (s, 2H, CH_2O), 6.51 (d, J_{trans} = 16.2 Hz, 1H, CHC=N), 6.97 (d, *J* = 8.4 Hz, 2H, H_{arom}), 7.22–7.43 (m, 13H, H_{arom} and CH(*p*-$BnOC_6H_4$)). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.8 (CH_2Ph), 67.7 (CHBn), 70.0 (CH_2Ph), 71.5 (CH_2O), 112.9 (CH), 115.1, 126.5, 127.4, 128.1, 128.5, 128.6, 129.0 (2), 129.1, 136.5, 138.0, 139.6 (CH), 159.9, 164.0 (C=N). HRMS (FAB$^+$): calculated for $C_{25}H_{24}NO_2$ [M+H]$^+$, *m*/*z* 370.1807; found for [M+H]$^+$, *m*/*z* 370.1820.

4.8.7. (4*S*)-4-Benzyl-2-(*p*-carbomethoxycinnamoyl)-2-oxazoline (*S*)-1g

(290 mg, 89%) as a white solid, mp 114–115 °C, $[\alpha]_D$ = +4.0 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (dd, *J* = 13.8, 8.7 Hz, 1H, CH_2Ph), 3.16 (dd, *J* = 13.8, 5.7 Hz, 1H, CH_2Ph), 3.92 (s, 3H, CH_3O), 4.06 (dd, *J* = 8.5, 7.5 Hz, 1H, CH_2O), 4.30 (dd, *J* = 9.3, 8.5 Hz, 1H, CH_2O), 4.52 (m, 1H, CHBn), 6.72 (d, J_{trans} = 16.2, 1H, CHC=N), 7.21–7.38 (m, 6H, H_{arom} and CH(*p*-$CH_3O_2CC_6H_4$)), 7.52 (d, *J* = 8.1 Hz, 2H, H_{arom}), 8.03 (d, *J* = 8.1 Hz, 2H, H_{arom}). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.7 (CH_2Ph), 52.2 (CH_3O), 67.8 (CHBn), 71.6 (CH_2O), 117.6, 126.5, 127.3, 128.6, 129.1, 130.0, 130.6, 137.8, 138.7, 139.5 (CH), 163.3 (C=N), 166.6 (C=O). HRMS (FAB$^+$): calculated for $C_{20}H_{20}NO_3$ [M+H]$^+$, *m*/*z* 322.1443; found for [M+H]$^+$, *m*/*z* 322.1430.

4.8.8. (4*S*)-4-Benzyl-2-(furan-2-yl-vinyl)-2-oxazoline (*S*)-1h

(180 mg, 94%) as a brown solid, mp 72–74 °C, $[\alpha]_D$ = +16.0 (*c* 1.0, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$): δ (dd, *J* = 13.8, 8.4 Hz, 1H, CH_2-Ph), 3.16 (dd, *J* = 13.8, 5.2 Hz, 1H, CH_2Ph), 4.01 (dd, *J* = 8.5, 7.5 Hz, 1H, CH_2O), 4.24 (dd, *J* = 9.0, 8.5 Hz, 1H, CH_2O), 4.49 (m, 1H, CHBn), 6.42-6.44 (m, 1H, H_{arom}) 6.48–6.57 (m, 2H, H_{arom} and CHC=N), 7.07–7.45 (m, 7H, H_{arom} and CH-furfuryl). ^{13}C NMR (75 MHz, $CDCl_3$): δ 41.6 (CH_2Ph), 67.6 (CHBn), 71.4 (CH_2O), 112.0, 112.7, 112.8, 126.4, 127.0, 128.5, 129.1, 137.8, 144.0, 151.3, 163.6 (C=N). HRMS (FAB$^+$): calculated for $C_{16}H_{16}NO_2$ [M+H]$^+$, *m*/*z* 254.1181; found for [M+H]$^+$, *m*/*z* 254.1187.

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